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Highly Chemoselective Reductive Amination by One Pot Reaction of Aldehydes, Amines and Dihydropyridine Catalyzed by TMSCl

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More efficient, cost effective and metal free DHP/TMSCl system for one pot reductive amination of aldehydes was developed. The method allows the efficient one pot synthesis of structurally diverse amines with Hantzsch ester as the hydrogen source in the presence of trimethylsilyl chloride as a catalyst in high to quantitative yields under mild conditions.

Keywords: Aldehydes, Amines, Dihydropyridine, Reductive amination, TMSCl

INTRODUCTION

Nonmetallic systems are efficient for catalytic reduction and are complementary to the metallic catalytic methods. For example, lithium aluminium hydride, sodium borohydride and borane-tetrahydrofuran have been extensively used as the most efficient and convenient reducing agent to prepare a wide range of pure compounds (*e.g.*, α-amino acids can be prepared from α-enamides, alcohols from ketones and amines from oximes or imines). Nevertheless, application of these protocols to sensitive, acid-labile or polyfunctional substrates is limited. On the other hand, in recent years, novel methods of substrate activation have been achieved using organic catalysts that can now deliver unique, orthogonal, or complementary selectivity in comparison with many established metal-catalyzed transformations. This renders the development of metal-free catalytic concepts for a mild direct reductive amination a very important research goal [1].

Amines and their derivatives exist in many biologically important molecules, and are important intermediates in the synthesis of pharmaceutically active substances, dyes, and fine chemicals [2]. In addition, optically active amines have important applications in asymmetric synthesis as chiral auxiliaries [3,4], catalysts [5], and resolving agents [6]. Consequently, efforts are focused on the development of a methodology for the simple and practical synthesis of amine derivatives in modern organic syntheses.

The direct reductive amination of aldehydes and ketones with metal hydride reagents is one of the most useful methods for the synthesis of secondary and tertiary amines and in recent years, different methods have been developed to carry out this transformation [7]. The choice of the reductant is very critical because the undesirable reduction of starting carbonyls must be suppressed [8].

However, most of these reagents may have some drawbacks. For examples, catalytic hydrogenation is incompatible with compounds containing a carbon-carbon double or triple bond and other reducible functional groups such as nitro, cyano and furyl. Cyanoborohydride and tin hydride reagents are highly toxic and generate toxic by-products such as cyanide or organotin compounds upon workup, which may result in the contamination of the product.

On the other hand, in recent years dihydropyridines were found to serve as mild, useful reagents capable of reducing

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organic substrates in the absence of metal ions under either thermal or acid-catalyzed conditions. Hantzsch dihydropyridine is readily obtained in multi-gram scale by the reaction of ammonia, formaldehyde, and two equivalents of ethyl acetoacetate in any laboratory without any difficulty [9]. Furthermore, organocatalyst-based reduction with dihydropyridine have received considerable attention in contrast to metal-based reductions in recent years, because complete removal of metal impurities from reaction products is often difficult but necessary, especially in the production of pharmaceutical intermediates and natural products due to toxicity problems [10].

In pursuit of our interest to develop organic transformation by using simple reagent, catalyst and reaction media [11], we have disclosed the chemoselective one-pot reductive amination of aldehydes using inexpensive, safe to handle and environmental friendly dihydropyridines (DHP) in the presence of a catalytic amount of trimethyl silyl chloride.

EXPERIMENTAL

General

^{1}H NMR spectra were recorded on 500 MHz NMR spectrometer and ^{13}C NMR spectra were recorded on 125 MHz NMR spectrometer respectively using $CDCl_3$, as a solvent (Chemical shifts have been expressed in ppm downfield from TMS). Melting points were measured on a Buchi Melting Point B-545 apparatus. Amines, aldehydes, TMSCl and the solvent, all commercially available, were purchased and used without further purification. Water and other solvents were distilled before use.

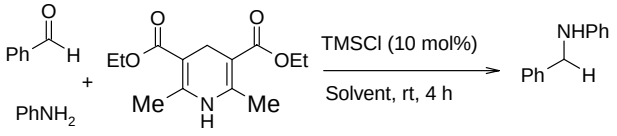
General procedure for reductive amination in the presence of trimethyl silyl chloride. To a stirred solution of amines (2 mmol) and aldehydes (2 mmol) in anhydrous CH_2Cl_2 (3 ml), dihydropyridine (2.5 mmol) and TMSCl (10 mol%) were added in one portion under argon. The reaction mixture was stirred for 3-8 h, then poured into saturated aqueous $NaHCO_3$ solution (20 ml) and extracted with CH_2Cl_2 (10 ml). The organic layer was washed with water (20 ml), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography or acidic workup to provide the corresponding pure product.

RESULTS AND DISCUSSION

To explore the possibility of the reductive amination of primary and secondary amines and aldehydes, a model reaction, between benzaldehyde and aniline was performed in the presence of TMSCl. By optimizing the solvent, reaction temperature and the amount of the reagents, the conditions shown in Scheme 1 were found to be suitable. In the absence of TMSCl, only a trace amount of imines and starting material was obtained. After optimization of reaction condition, we then studied the general applicability of this procedure for the synthesis of sterically, electronically, and functionally diverse amines (Table 1). The data in Table 1 show that different aldehydes are successfully converted to the corresponding amines in high yields at room temperature. The presence of electron-withdrawing or electron-donating substituents on the aromatic ring did not affect the course of the reaction. Sensitive functionalities such as OMe and NO_2 were tolerated under the mild reaction conditions.

The scope of our method could be extended to other amines. In the case of amines having an electron-donating group such as 4-methoxy aniline and 4-buthyl aniline the corresponding products were obtained in good yields. Especially, sterically hindered amines, 2,4,6-trimethyl anilines, developed the corresponding products in moderate yields. Furthermore, electron-withdrawing amines such a 4-chloroaniline and 3,4-dichloroaniline launched the desired products in good yields.

Moreover, the data in Table 1 clearly show that the reaction of different aliphatic amines such as diethylamine, pyrrolidine or piperidine with benzaldehyde produces the corresponding

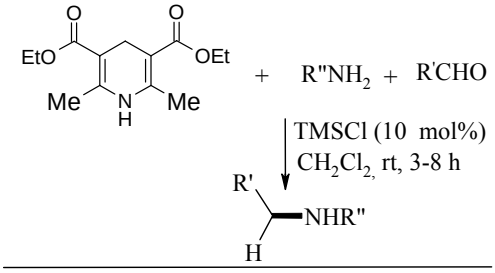


Solvent	CH_2Cl_2	$ClCH_2CH_2Cl$	CH_3CN	Ether	THF	Toluene
Yields (%)	95	90	40	35	45	92

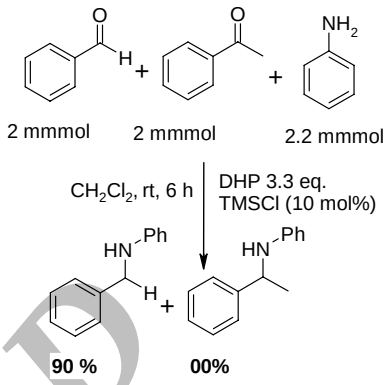
benzaldehyde, 2 mmol, aniline, 2 mmol, DHP, 2.5 mmol

Scheme 1. Optimization of reaction conditions

Table 1. One Pot Reductive Amination of Aromatic Aldehydes



Entry	R'	R"	Yields%
1	Ph	4-ClC_6H_4	90
2	Ph	Ph	95
3	Ph	4-BrC_6H_4	92
4	4-ClC_6H_4	Ph	90
5	4-ClC_6H_4	4-ClC_6H_4	92
6	4-ClC_6H_4	4-IC_6H_4	83
7	3-$NO_2C_6H_4$	4-IC_6H_4	80
8	3-$NO_2C_6H_4$	4-ClC_6H_4	80
9	3-$NO_2C_6H_4$	Ph	82
10	3-$NO_2C_6H_4$	3-*i*-*pr*Ph	85
11	4-$NO_2C_6H_4$	4-ClC_6H_4	80
12	4-$NO_2C_6H_4$	4-BrC_6H_4	93
13	2,4-diClC_6H_3	3,4-diClC_6H_3	80
14	4-ClC_6H_4	3,4-diClC_6H_3	75
15	2,4-diClC_6H_3	4-ClC_6H_4	75
16	2,4-diClC_6H_3	Ph	80
17	3-$MeOC_6H_4$	Ph	77
18	4-ClC_6H_4	4-$OMeC_6H_4$	77
19	4-$CO_2MeC_6H_4$	Ph	90
20	4-$CO_2MeC_6H_4$	4-ClC_6H_4	88
21	4-ClC_6H_4	4-BuC_6H_4	90
22	4-ClC_6H_4	2,4,6 trimetylC_6H_2	70
23	2,4-diClC_6H_3	4-ClC_6H_4	75
24	2-Furyl	Ph	78
25	2-Thienyl	Ph	75
26	Ph	Pyrrolidine	95
27	Ph	Pypiridine	95
28	Ph	Diethylamine	92



Scheme 2. Selective amination of benzaldehyde with aniline in the presence of acetophenone

amines in high yields at room temperature. The reactions are clean and highly selective, affording exclusively the desired yields in short times. The reaction conditions are mild enough to perform these reactions in the presence of either acid or base sensitive functional groups. Furthermore, this method is equally effective for aromatic, hindered, and unhindered amines. The yields of products were not affected by the nature of amines.

This method is highly selective for the preparation of amines from aldehydes. Thus, reductive amination of an aldehyde in the presence of a ketone, using TMSCl as the catalyst in CH_2Cl_2 at room temperature, gave only secondary amine from aldehyde and ketone remained intact (Scheme 2). In conclusion, in this article we have reported amination of aromatic and aliphatic aldehydes with primary and secondary amines using DHP as a reducing agent catalyzed with TMSCl at room temperature in good to excellent yields. We believe this methodology to be a useful addition to the available methods regarding this transformation.

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REFERENCES

[1] S.J. Connon, Org. Biomol. Chem. (2007) 3407.

[2] T. Henkel, R.M. Brunne, H. Mueller, F. Reichel, Angew. Chem. Int. Ed. 38 (1999) 643.

[3] K.W. Henderson, W.J. Kerr, J.H. Moir, Chem. Commun. (2000) 479.

[4] V. Gotor-Fernandez, P. Fernandez-Torres, V. Gotor, Tetrahedron Asy. 17 (2006) 2558.

[5] M.F.A. Adamo, V.K. Aggarwal, M.A. Sage, J. Am. Chem. Soc. 122 (2000) 8317.

[6] J.W. Nieuwenhuijzen, R.F.P. Grimbergen, C. Koopman, R.M. Kellogg, T.R. Vries, E. Van Echten, B. Kaptein, L.A. Hulshof, Q.B. Broxterman, Angew. Chem. Int. Ed. 41 (2002) 4281.

[7] a) T. Suwa, I. Shibata, K. Nishino, A. Baba, Org. Lett. 1 (1999) 1579; b) C.F. Lane, Synthesis (1975) 135 and references cited therein; c) H. Firouzabadi, N. Iranpoor, H. Alinezhad, Bull. Chem. Soc. Jpn. 76 (2003) 143; d) H. Firouzabadi, N. Iranpoor, H. Alinezhad, Synth. Commun. 32 (2002) 3575; e) I. Shibata, T. Moriuchi Kawakami, D. Tanizawa, T. Suwa, E. Sugiyama, H. Matsuda, A. Baba, J. Org. Chem. 63 (1998) 383; f) R. Apodaca, W. Xiao, Org. Lett. 3 (2001) 1745.

[8] a) T. Gross, A.M. Seayad, M. Ahmad, M. Beller, Org. Lett. 4 (2002) 2055; b) P.S. Reddy, S. Kanjilal, S. Sunitha, R.B.N. Prasad, Tetrahedron Lett. 48 (2007) 8807; c) H. Kato, I. Shibata, Y. Yasaka, S. Tsunoi, M. Yasuda, A. Baba, Chem. Commun. (2006) 4189; d) S. Hoffmann, M. Nicoletti, B. List, J. Am. Chem. Soc. 128 (2006) 13074; e) D. Menche, J. Hassfeld, J.J. Li, G. Menche, A. Ritter, S. Rudolph, Org. Lett. 8 (2006) 741; f) H. Firouzabadi, B. Zeynizadeh, Bull. Chem. Soc. Jpn. 70 (1997) 55; g) H. Firouzabadi, M. Adibi, Phosphorous, Sulfur and Silicon 142 (1998) 125; h) C. Salmi, C. Loncle, Y. Letourneux, J.M. Brunel, Tetrahedron 64 (2008) 4453; i) R.Y. Lai, C.I. Lee, S.T. Liu, Tetrahedron 64 (2008) 1213; j) T. Mizuta, S. Sakaguchi, Y. Ishii, J. Org. Chem. 70 (2005) 2195; k) M.R. Saidi, R. Stan Brown, A. Ziyaei-Halimjani, J. Iran. Chem. Soc. 4 (2007) 194; l) H. Firouzabadi, N. Iranpoor, H. Alinezhad, J. Iran. Chem. Soc. 6 (2009) 177.

[9] a) M.A. Zolfigol, M. Mokhlesi, J. Iran. Chem. Soc. 5 (2008) 91; b) A. Saini, S. Kumar, J. Sandhu, J. Sci. Ind. Res. 67 (2008) 95; c) J.-J. Xia, G.-W. Wang, Synthesis (2005) 2379.

[10] a) P.T. Franke, R.L. Johansen, S. Bertelsen, K.A. Jorgensen, Chem. Asian J. 3 (2008) 216 and references cited therein; b) S.G. Ouellet, A.M. Walji, D.W.C. Macmillan, Acc. Chem. Res. 40 (2007) 1327 and references cited therein; c) T. Itoh, K. Nagata, A. Kurihara, M. Miyazaki, A. Ohsawa, Tetrahedron Lett. 43 (2002) 3105; d) D. Menche, J. Hassfeld, J. Li, G. Menche, A. Ritter, S. Rudolph, Org. Lett. 8 (2006) 741; e) R. Kadyrov, T.H. Riermeier, Angew. Chem., Int. Ed. 42 (2003) 5472.

[11] a) N. Azizi, F. Aryanasab, L. Torkiyan, A. Ziyaei, M.R. Saidi, J. Org. Chem. 71 (2006) 3634; b) N. Azizi, L. Torkiyan, M.R. Saidi, Org. Lett. 8 (2006) 2079; c) N. Azizi, M.R. Saidi, Org. Lett. 7 (2005) 3649; d) N. Azizi, M.R. Saidi, Tetrahedron 63 (2007) 888; e) N. Azizi, M.R. Saidi, Organomet. 23 (2004) 1457; f) N. Azizi, A. Khajeh Amiri, M. Bolourtchian, M.R. Saidi, J. Iran. Chem. Soc. 6 (2009) 749; g) N. Azizi, E. Akbari, M.R. Saidi, J. Iran. Chem. Soc. 6 (2009) 165.